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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	PAPER NUMBER
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,563	MATHEUS ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8-15 and 17-22* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-15 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/12/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 12 September 2008 are acknowledged. Applicants have canceled claims 4-7 and 16 and added new claims 19-22. Thus, claims 1-3, 4-15 and 17-22 are pending. Claims 17 and 18 have been amended and are now drawn to a different invention than originally presented. Newly amended claims 17 and 18 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims were drawn to use of the crystallized antibodies in the preparation of a medicament. However, the currently amended claims are now drawn to a method of treating by administering the crystallized antibodies and are thus no longer drawn to the same invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 17 and 18 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Said claims, however, may be subject to rejoinder should the products be found allowable. Thus, claims 1-3, 4-15 and 19-22 are subject to examination on the merits.

Priority

2. Applicants have provided a copy of a translation of the foreign priority document and the required statements pursuant to MPEP 201.15. The priority date for prior art purposes is thus 29 November 2003.

3. Applicant have stated that USPTO Patent Application Information Retrieval (PAIR) indicates the filing date of the International Application PCT/EP04/12837 is May 25, 2006 and that this is incorrect. It is stated that the filing date should be December 11, 2004

However, the BibData sheet submitted previously provides the accurate information regarding the instant application, e.g. PCT/EP04/12837 was filed December 11, 2004 and the 371(c) date, or in other words, the date in which the PCT application was filed as a national stage application here at the USPTO is May 25, 2006. The continuity data section of PAIR indicates the date is the Parent filing date ***OR*** the 371(c) date. The date listed apparently is the 371(c) date as noted above and is accurate. This does not affect the priority date of the PCT application.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 12 September 2008 has been being considered by the examiner. See initialed and signed PTO-1449. It still noted that all foreign references listed on the previous IDS (05/26/2006) still have not been considered as Applicants have not provided said references.

Withdrawal of Rejections/Objections

5. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

6. The objection to the specification is withdrawn in view of Applicants amendments to specification to update the Cross-Reference to Related Applications information.

7. The objection to claims 1-3 and 6-18 are withdrawn in view of Applicants amendments to recite anti-EGFR as 'anti-epidermal growth factor receptor' in claim 1.

8. The rejection of claims 16-18 under 35 U.S.C. 112 2nd paragraph and 101 is withdrawn. Claim 16 is cancelled and claims 17 and 18 have been amended to recite Method claims rather than "Use" claims.

9. The rejection of claims 13-15 under 35 U.S.C. 112 2nd paragraph for being indefinite for lacking antecedent basis is withdrawn in view of the amendment to the claims.

10. The rejection of claims 1-3, 6-10, 12-14 and 16-18 under 35 U.S.C. 102 (e) as anticipated by Kussie et al. is withdrawn as Applicants have provided a certified translation of the foreign priority document. Thus, said intervening reference is no longer considered prior art.

11. The rejection of claim 13 as anticipated under 35 U.S.C. 102(e) by Mahler et al. (US 2004/0170632) is withdrawn because Applicants have provided a certified translation of the foreign priority document thus making the priority date September 29, 2003. Because the PCT/EP02/06696 (filed June 18, 2002) application, to which Mahler et al. claim priority, was published as a WO document in German, said date is not available as a 102(e) prior art date.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement – Biological Deposits:

13. Claims 1-3, 6-15 and new claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For Applicants convenience, the rejection is re-stated below.

It is apparent that anti-EGFR antibodies are required to practice the claimed invention. As required elements, *ALL anti-EGFR antibodies encompassed by the claims must be known and readily available to the public or obtainable by a repeatable method set forth in the specification*. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of

the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant is reminded that the following and should amend the specification accordingly.

The current address of the ATCC is as follows:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

In the instant application, it is noted that the only anti-EGFR antibody used in the specification to make solid crystal anti-EGFR antibodies is Erbitux™, also known as MabC225 or cetuximab. Nonetheless, EMD 72000/matuzumab/Mab h425 is claimed as well. While these antibodies *may be* publicly available for purchase, although Applicants do not say as much, the restrictions and assurances made by the owners of

these products, which are directed to US patent 6217866 and US patent 5558864 (both cited on the instant IDS), have not been made on the instant record. As such, Applicants are required to indicate how the assurances and restrictions with regard to the public availability of these two anti-EGFR antibodies, as required and set forth above will be irrevocably removed should the instant application be allowable and issue as a United States patent.

Response by Applicants and Examiner's Rebuttal:

Applicants traverse the enablement rejection regarding the Deposit of Biological Materials and the corresponding assurances that are required by stating that a biological deposit is not necessary if the required biological materials can be obtained from publicly available material through only routine experimentation.

However, Applicant have not provided any evidence that the material is publicly available without any restrictions. While patents 5,558,864 and 6,217,866 have been issued and the specifications state that the hybridoma cell lines have been deposited with the ATCC, this is not enough to show that all restrictions imposed by the depositor on the availability to the public of the deposited material has been irrevocably removed upon the granting of said U.S. patents. MPEP 2404.01 specifically states:

> "The mere reference to a deposit or the biological material itself in any document publication does not necessarily mean that the deposited biological material is readily available. ***Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires,*** *with one possible exception (37 CFR 1.808(b)),* ***that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent***. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Since the assignee of the at least the '864 patent are one and the same, it should be fairly simple for Applicants to provide the required evidence to clarify the instant record that the necessary restrictions on the accessibility (e.g. that ALL restrictions have been irrevocably removed) of the deposit were removed upon the granting of said '864 patent at least. However, it should be noted, that a cursory review of the latest version of the ATCC Hybridoma Cell Line Index does not even list deposit HB 9629 (see attached) as a publicly available product thus further highlighting the necessity of public availability of cell lines in the instant application.

As far as the '866 patent is concerned the deposits of ATCC Nos. HB 9763 and 9764, while these are listed on said ATCC index, will also require that the assurances were satisfied and removed during patent prosecution. Applicants are also encouraged to clarify which deposits relate to cetuximab and to EMD72000, respectively.

Scope of Enablement:

Should the above deposit requirement and/or removal of restrictions along with the assurances be satisfied, the following 112 1st paragraph rejections apply.

14. Claims 1-3, 6-15 and new claims 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for solid crystals of whole murine humanized monoclonal antibodies of Erbitux/MabC225/cetuximab Erbitux™/MabC225/Cetuximab produced by very specific crystallization methods and

conditions of Example 2 and 3 only, does not reasonably provide enablement for crystals of variants or fragments thereof or for crystals of Mab h425/EMD 72000/matuzumab antibodies, variants or fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to crystals of anti-EGFR antibodies of cetuximab or Mab h425 and made by precipitating an aqueous solution of said antibodies by means of a precipitating agent. However, the specification *only* sufficiently describes crystals that have been produced by the specific examples described in Examples 2 and 3 which discloses using Erbitux™ at a concentration of 20mg/ml in either 10 mM phosphate buffer at pH 8.0 or 10 mM citrate buffer at pH 5.5, adding either 10 mM phosphate buffer pH 8.0 to the phosphate protein solution or 10 mM citrate buffer pH 5.5 to the citrate protein solutions, respectively, and finally adding saturated ammonium sulfate in 10 mM phosphate buffer pH 8.0 to the phosphate protein-buffer solution or 50% v/v ethanol in 10 mM citrate buffer pH 5.5 to the citrate protein-buffer solution, respectively (it is noted that all additions are phosphate buffers to phosphate buffers and citrate buffers to citrate buffers/salts) and shaking this solution by hand for an undisclosed period of time at either room temperature or 4°C. It is presumed that the anti-EGFR antibody humanized monoclonal antibody Erbitux™ used in the crystallization procedures of Examples 2 and 3 is commercially purchased but this is not disclosed. Beyond this scope, however, the specification and claims are not sufficiently enabled for a skilled artisan not to have to endure a considerable amount of undue experimentation

because: a) the specification does not disclose crystallization of fragments or variants of cetuximab, b) the specification does not disclose crystallization of Mab h425, variants or fragments thereof and c) there is considerably unpredictability in crystallizing any protein or antibody to begin with. Furthermore, the specification states that this is the first time any anti-EGFR antibody has been crystallized, especially, Erbitux/MabC225/Cetuximab and thus there is no prior art teachings a skilled artisan can rely upon for help or guidance beyond the prior art which falls between the foreign priority date and the effective filing date of the instant PCT (see 35 USC 102(e) rejection below). Thus, a skilled artisan, in order to achieve the full scope of that which is being claimed, would be required to practice undue experimentation. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant case, the quantity of experimentation would be considerable because the smallest change in ***any*** parameter in crystallizing a protein/antibody can have enormous consequences. Thus, it is not enough to have the crystallization conditions of a related/similar protein/antibody or 'native' protein/antibody. Rather, what would be required is precise instruction about how to make each and every cetuximab and Mab h425 crystals and variants and fragments thereof in order to avoid undue experimentation, and this includes precise instruction of how the protein/antibody was exactly produced and exactly purified, which include the noted assurances of public availability as noted above. However, beyond that which is described in Examples 2 and 3, there is no adequate direction or guidance in the specification of how a skilled artisan might achieve crystal growth of any other anti-EGFR antibody in any other conditions or with any other crystallization techniques (e.g. microbatch, macrobatch, sitting drop, capillary liquid-liquid diffusion etc.). The nature of the invention and of the prior art suggests that crystallizing proteins and antibodies is an extremely tenuous science; what works for one protein or antibody does not necessarily for another, and what works for one native protein or antibody does not necessarily work for a mutant or fragment even though they essentially contain the same protein/antibody that has

already been crystallized. It is noted that Applicants attempted to crystallize Erbitux™ using a commercially available crystallization grid matrix screen, Crystal Wizard I, and were only able to successfully produce salt crystals (see Example 8). Thus, this also lends weight to the fact that crystallization of proteins and antibodies is not straight forward and is unpredictable at best. Specific overexpression protocols, precise protein purification protocols and exact crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein and/or antibody (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22).

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex even though they contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein complex). McPherson (Eur. J. Biochem. 1990, 189:1-23) outlines 25 different parameters which do or could affect the crystallization of any protein (see Table 2, p. 13). It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

> "Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids. There are even cases where the identical protein prepared by different procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins."

Thus, *at best*, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful for a single protein. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). Furthermore, the prior art is of little assistance because while other antibodies have been crystallized, no anti-EGFR antibodies in any form (e.g. Fab fragments, single chain antibodies, etc.) have been successfully produced. Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

Therefore, claims to all fragments and derivatives of cetuximab, Mab h425 crystals and fragments and derivatives thereof made by broad product by process, are not fully enabled beyond that described in Examples 2 and 3 for the whole murine humanized monoclonal antibody of Erbitux/MabC225/cetuximab.

Response by Applicants and Examiner's Rebuttal:

Applicants traverse the above rejection and submit that the specification, coupled with a skilled worker's knowledge, provides adequate guidance to make and use the instantly

claimed compounds. It is further stated that a skilled biochemist who is equipped with the claimed antibody molecules and who is familiar with the techniques and/or reagents used in crystallography would possess a definitive understanding of what is described in Applicants' claims. The claimed antibody molecules, for example, chimeric monoclonal antibody c225 or a humanized monoclonal antibody h425 were well-appreciated in the art prior to the filing date of the present application. Applicants also assert that because it is well known in the art how to make fragments or derivatives of antibodies, that a skilled artisan would not need undue experimentation to make antibody crystals thereof. (see Remarks, pp. 11-12)

However, in the terms of protein/antibody crystallography, a product can be well known for decades and never be amenable to crystallization. The Examiner is well aware that both antibodies, chimeric monoclonal antibody c225 or a humanized monoclonal antibody h425 were and indeed are well known. This is not disputed. However, what is non-enabling is the unpredictability of crystallizing any protein or antibody, even those derivatives or variants wherein the wild-type protein/antibody has previously been crystallized before. As taught by McPherson et al., there are over 25 different parameters affecting the success in crystallizing polypeptide/macromolecules such as proteins and antibodies and varying even one or two amino acids can change all of the parameters and one is forced to start again from scratch. Furthermore, while Applicants have disclosed at least how to make full length, unfragmented cetuximab, there is no disclosure or guidance whatsoever for Mab h425 and thus one skilled in the art does not even have a single example of where to begin or start because there is no

expectation in this particular art that what works for one type of antibody/protein has any sort of relevance whatsoever for a completely different protein/antibody.

As such, the scope of the claims exceeds that which is enabled by the specification and knowledge/unpredictability in the art.

Written Description:

15. Claims 1-3, 6-15 and new claims 19-22 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a broad genus of any crystal of anti-EGFR antibody crystals, and those in pharmaceutical compositions and methods of making thereof. While the structure and function of some a single species of said genera of anti-EGFR antibody crystals is disclosed in the specification, the common characteristics of the species that define said genera are not described. Furthermore, the genus of anti-EGFR antibodies is very broad and diverse and the single species of Erbitux/MabC225/cetuximab described in the specification in crystalline form is not representative of this entire genus of solid crystal anti-EGFR antibodies.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials."

University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes a single species of Erbitux/MabC225/cetuximab crystals that are produced by a batch method which produces crystals from slightly different conditions that fall within the instant genera of crystals. Examples 2 and 3 describe the precise antibody/protein concentration and the buffer which said antibody is in and the exact crystallization conditions which results in crystals. Example 2 used 10 mM phosphate buffers at pH 8.0 and saturated ammonium sulfate in the same phosphate buffer to produce crystals whereas Example 3 used 10 mM citrate buffer at pH 5.5 and 50% ethanol in the same citrate buffer to produce crystals of Erbitux/MabC225/cetuximab. These two examples sufficiently and full describe a single species of anti-EGFR antibody crystals. However, these species do not sufficiently describe the entire genus of cetuximab variant or fragment crystals, nor the genus of

Mab h425 crystals (e.g. whole anti-body, variants and fragments thereof) antibody crystals.

In general, for a species of crystal to be adequately described, the following must be adequately disclosed in the specification and the claims: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein/antibody (preferably a SEQ ID NO of all included residues) and any molecule bound to it) (2) the exact protein concentration and buffer the protein/antibody is in, (3) the exact temperature, buffers, salts, additives used for crystallization and 4) the technique used to obtain the crystal (e.g. vapor diffusion, microbatch, liquid-liquid diffusion, etc). The Erbitux/MabC225/cetuximab crystal species noted above have adequately met this burden. However, the process of obtaining the crystals which is encompassed by the breadth of the claims is not described sufficiently. A singular chemical composition can crystallize differently based on the crystallization conditions and techniques used (see, for example, Applicants failed attempts in Example 8). For example, if a skilled artisan wants to crystallize Erbitux/MabC225/cetuximab for structural studies, then the crystallization technique, buffer considerations, temperatures, etc. are going to very different than trying to crystallize a protein/antibody for therapeutic use because the overall objectives are so different and the quality of the crystals are important. While the instant claim broadly describes a process of precipitating the antibody solution with a precipitating agent, this is not enough.

However, based on the instant the specification, the chemical composition, the process of obtaining anti-EGFR antibodies in the first place, along with the process of

obtaining crystals thereof, which are encompassed by the breadth of the claims is unpredictable to one of skill in the art. One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of anti-EGFR antibody crystals are also not adequately described and the single species of Erbitux/MabC225/cetuximab crystals which fall within the structurally and functionally diverse genus is not deemed representative to claim the entire broad genus of anti-EGFR antibody crystals.

Response by Applicants and Examiner's Rebuttal:

Applicants assert that the amendments to claims overcome the written description rejection or record; however, to the extent said rejection is maintained, provide arguments in support of their assertions.

Applicants state that it is the Examiner's position that the central tenant of the rejection is that the central contention with respect to the written description rejection pertains to the nature and/or description of the antibody molecules recited in the claims. Applicants further summarize the decision by the courts for Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo Biochem II") establishes a legal precedent for written description of antibody molecules and further summarize the Written Description guidelines as set forth by USPTO which, for example, would find compliance with 112, ¶ 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional

characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.

While the Examiner is not contesting these well known facts for satisfying the written description of antibodies in isolated form, produced by an ATCC deposited hybridoma, etc., indeed this has been well established in the courts, the Examiner is asserting that these decisions are not applicable to antibodies in crystalline form. It is noted that the courts also have established that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895; especially in those arts which are highly unpredictable. See for example, the decision for *Eli Lilly* wherein the courts stated: "In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ..." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.
Thus, the Examiner is **not** asserting that it is the antibody art which is unpredictable but rather it is the art of crystallizing any protein/macromolecule, including antibodies, which is highly unpredictable.

Applicants submit that because they have described how to obtain one species of antibody crystals encompassed within the broad and variable genus of crystals as claimed, and because these antibodies are in fact patented, that this puts Applicants in

possession of the claimed invention. However, as noted above, it does not put them in possession of the genus of *crystallized* forms of these antibodies.

As such, the written description rejection of record is maintained.

New Rejections – Not Necessitated by Amendment

Claim Rejections - 35 USC § 112 – 2nd

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are dependent upon claim 1 which states a ***crystal*** of a chimeric monoclonal antibody c225 or a humanized monoclonal antibody h425. However, claim 13 recites that the crystal of claim 1 is crystalline form, *soluble form or suspended form.* Claim 14 states said crystal is in *soluble form or suspended form.* However, once a crystal is soluble form or even suspended form, it ceases to be a crystal. Thus, these limitations are both deemed indefinite, as well as lack antecedent basis, because claiming something which is physically impossible, e.g. being in a physical crystal state and in a soluble state at the same time, makes said limitations indefinite.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al. (US 2002/0197261).

Li et al. teach a soluble pharmaceutical composition wherein 50 mg of Cetuximab is added to 5 ml of PBS, which a pharmaceutically acceptable buffer, to thus yield a pharmaceutical composition having a concentration of 10 mg/ml (see paragraph 0088). Since the claims state that the composition can be in soluble form, then the teaching of Li et al. meets the limitations of the claims.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suzanne M. Noakes/
Primary Examiner, Art Unit 1656
17 December 2008